REMARKS

Claims 16, 48, 49, and 52 have been canceled without prejudice.

Claims 1, 38, and 41-43 have been amended to delete the phrase "wherein the immunogen is not an antibody." Claim 43 has also been amended to add the phrase "an immunogen conjugated to a folate receptor-binding ligand selected from the group consisting of folate and analogs thereof," and to delete the phrase "ligand-immunogen conjugate." Support for the amendments to claim 43 can be found throughout the specification, for example, on page 10, lines 21-22 of the specification. Minor amendments have also been made to claims 38, 41, and 42. Applicants acknowledge that these amendments are being made after final rejection and that entry of amendments after final are at the Examiner's discretion. They were not presented earlier because these amendments were not necessary to complete response to the last Official Action. Further the amendments are responsive to the Examiner's comments in the present Official Action, and they put the claims in condition for allowance or in better form for appeal, and they do not raise any new issues or require further search. Applicants respectfully request that the Examiner exercise her discretion in favor of entry of the amendments under these circumstances.

The Examiner has rejected claims 43-46 under 35 U.S.C. § 112, ¶ 1, for lack of enablement. The Examiner contends that the specification is enabling for a method dependent on molecules which bind to the folate receptor, but not for vitamins that bind receptors which are not the folate receptor. Applicants do not acquiesce to the Examiner's reasons for rejection, but claims 43-46 have been amended to specify that the ligand is "a folate receptor-binding ligand selected from the group consisting of folate and analogs thereof" to expedite prosecution of the application. Withdrawal of the rejection of claims 43-46 under 35 U.S.C. § 112, ¶ 1, is respectfully requested.

Claims 1, 8-10, 13, 16, 18-38, 41-46, and 48-53 stand rejected under 35 U.S.C. § 112, ¶ 1, for failing to comply with the written description requirement. Claims 16, 48, 49,

and 52 have been canceled without prejudice. Claims 1, 8-10, 13, 18-38, 41-46, 50-51, and 53 have been amended to delete the phrase "wherein the immunogen is not an antibody" in an attempt to respond to the Examiner's rejection under 35 U.S.C. § 112, ¶ 1. Support for claim 53 can be found on page 12, lines 26-28. Although the rejected claims have been amended, Applicants do not acquiesce to the Examiner's reasons for rejection. Withdrawal of the rejection of claims 1, 8-10, 13, 18-38, 41-46, 50-51, and 53 under 35 U.S.C. § 112, ¶ 1, is respectfully requested.

Applicants have deleted the phrase "wherein the immunogen is not an antibody" from claims 1, 38, and 41-43. This phrase was added to claims 1, 38, and 41-43 in Applicants' response filed on September 22, 2003, and an argument was presented in the Septemeber 22 response that this amendment overcame the rejection of claim 43 under 35 U.S.C. § 102(b) over Krantz et al. As stated, in the present response, the phrase "wherein the immunogen is not an antibody" has been deleted from claim 43. Krantz et al. discloses a ligand-immunogen conjugate wherein, according to the Examiner, the immunogen is an antibody that binds to T cells. The antibody described in Krantz et al. is an anti-T cell antibody. Claim 43 specifies a composition comprising both 1.) a ligand-immunogen conjugate and 2.) a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the ligand-immunogen conjugate, and methods of treatment using these compositions. "A compound capable of stimulating an endogenous immune response wherein the compound does not bind to the ligand-immunogen conjugate" is a required element of claim 43. Krantz et al. fails to describe this required element of claim 43, and, thus, Krantz et al. cannot anticipate claim 43.

Furthermore, the amendment deleting the phrase "wherein the immunogen is not an antibody" was made in Applicants' response filed on September 22, 2003 to overcome the rejection of claims 1-8, 13, 26, 36, 43, and 47 under 35 U.S.C. § 102(b) as being anticipated by Roy et al. Claims 1, 8, 13, 26, 36, and 43 are remaining. Roy et al. discloses a

method of targeting tumor cells using a ligand-immunogen conjugate wherein the immunogen is an anti-T cell receptor antibody that pulls T cells to the site of the tumor by antibody binding to the T cells. Roy et al. also discloses the administration of staphlococcal enterotoxin β. Applicants' claimed method employs ligand-immunogen conjugates wherein the immunogen stimulates an endogenous immune response. For example, cells of the immune system that express Fc receptors on their surfaces may bind to the Fc portion of an endogenous antibody bound to the immunogen and an endogenous immune response, such as antibody-dependent cell-mediated cytotoxicity (*i.e.*, ADCC), directed to the cancer cells, may be stimulated. Alternatively, the immunogen may be recognized directly by a preexisting immune cell primed to recognize the immunogen and an endogenous immune response, directed to the cancer cells, may be stimulated.

Roy et al. describes the use of a ligand-antibody conjugate that pulls T cells to the site of tumor cells. Clearly, the Roy et al. method of inducing an immune system-mediated killing of a population of pathogenic cells is readily distinguishable from Applicants' claimed method; the method described in Roy et al. results in stimulation of an unnatural "immune response" (*i.e.*, T cells are pulled to the site of the tumor cells by binding to the anti-T cell receptor antibody). In contrast to the method described in Roy et al., Applicants' claimed method is effective to stimulate natural immune responses resulting in killing of the cancer cell population. Thus, Roy et al. does not describe a method of stimulating an endogenous immune response-mediated elimination of a population of cancer cells and Roy et al. cannot anticipate pending claims 1, 8, 13, 26, 36, and 43.

Claims 43, 45, and 46 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Cowan in view of Smith and Insel. The Examiner contends that Cowan discloses the use of a composition containing a ligand-immunogen conjugate to target cancer cells, and that Smith and Insel disclose the administration of cytokines to stimulate an endogenous immune response. Applicants respectfully traverse the Examiner's rejection.

Claims 43, 45, and 46 are not obvious under 35 U.S.C. § 103(a) over Cowan in view of Smith and Insel.

Applicants respectfully contend that the Examiner has not established a *prima facie* case of obviousness because the Examiner has not explained why the Examiner's proposed modifications to the method disclosed in Cowan to obtain Applicants' claimed invention would be obvious. Establishment of a *prima facie* case of obviousness under 35 U.S.C. § 103 under the test articulated by the Supreme Court in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 49 (1966) requires that the Patent Office:

1) set forth the differences in the claim over the applied references;

2) set forth the proposed modification of the reference or references which would be necessary to arrive at the claimed subject matter; and

3) explain why the proposed modification would be obvious.

To satisfy Step 3, the Examiner must identify where the prior art provides a motivating suggestion to make the modifications proposed in Step 2. *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992). The mere fact that the prior art may be modified as suggested by the Examiner does not make the modifications obvious unless the prior art suggests the desirability of the modification, *In re Fritch*, 922 F.2d 1260, 23 U.S.P.Q.2d 780 (Fed. Cir. 1992). Respectfully, Applicants contend that the Examiner has not made and articulated the requisite factual determinations properly antecedent to a rejection under § 103 especially with respect to explaining how the prior art suggests the desirability of the modification.

As discussed above, the Examiner indicates that Cowan discloses the use of a composition containing a ligand-immunogen conjugate to target cancer cells. The Examiner also indicates that Smith teaches the administration of cytokines along with folic acid analogs, and that Insel teaches that cytokines activate macrophages and B-cells. Although

the Examiner contends that Smith teaches the use of cytokines along with folic acid analogs, the folic acid analogs described in Smith are simply used as an additional therapeutic factor for administration with cytokines. The folic acid analogs described in Smith are not conjugated to an immunogen and there is no suggestion in Smith of administering cytokines along with folic acid analogs conjugated to an immunogen. Furthermore, neither Cowan nor Insel suggest the desirability of using cytokines in combination with a ligand-immunogen conjugate to stimulate the immune response. Accordingly, Applicants contend that the Examiner has not established a *prima facie* case of obviousness because the Examiner has not explained why the Examiner's proposed modifications to the method disclosed in Cowan to obtain the invention of Applicants' claims 43, 45, and 46 would be obvious. Although the prior art may be modified as suggested by the Examiner, the modification of the therapy described in Cowan to include the cytokines described in Smith and Insel is not obvious because none of these references mentions or provides any suggestion of combining a ligand-immunogen conjugate with cytokines to treat cancer cells. Accordingly, the invention of claims 43, 45, and 46 cannot be *prima facie* obvious over Cowan in view of Smith and Insel.

In the alternative, even if the Examiner has established a *prima facie* case of obviousness, and again Applicants contend that *prima facie* obviousness has not been established, the Examiner's § 103 rejection has been overcome based on the unexpected results (*i.e.*, the unexpected synergism) obtained with Applicants' claimed methods and compositions for use in targeting cancer cells.

The question of nonobviousness must turn on whether the *prima facie* case of obviousness of the claimed composition is rebutted by a showing of unexpected results. *In re Diamond*, 53 CCPA 1172, 360 F.2d 214, 149 USPQ 562 (1966). *In re Meinhardt*, 55 CCPA 1000, 392 F.2d 273, 157 USPQ 270 (1968). Synergism is an example of an unexpected result. The courts have defined synergism as an effect where the "whole in some way exceeds the sum of its parts," or when the combination produces a "new or different

function," or "unusual or surprising consequences." *Philips Industries Inc. & Mobil Temp. Inc. v. State Stove & Manufacturing Co., Inc.*, 522 F. 2d 1137 (6th Cir. 1975). Furthermore, as stated in MPEP § 716.02(a), "[e]vidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (*i.e.*, demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989)." Thus, a synergistic effect is an effect which is greater than the sum the effects of the individual components of a composition. As stated on page 22, lines 14-17 of the specification in reference to Example 7, "[t]he results shown in Figure 7 demonstrate that the capacity of folate-FITC and IL-2 to promote long-term survival of tumor-bearing mice is strongly synergistic with low-dose IL-2 alone having a negligible effect on the survival of the mice in the absence of folate-FITC and with folate-FITC having only a minor effect." Furthermore, as stated on page 28, lines 1-2, in reference to Example 16, "[t]hese results show that IFN-α, like IL-2, acts synergistically with folate-FITC to promote long-term survival of tumor-bearing mice."

Moreover, as shown by the results discussed in Examples 7 (see Fig. 7) and 16 (see Fig. 16), strong synergism is obtained with Applicants' claimed invention. In both Examples 7 and 16 a negligible effect was obtained with cytokines alone and a minor effect was obtained with the ligand-immunogen conjugate, but a strong synergistic effect was obtained with the combination of cytokines and the ligand-immunogen conjugate. A careful review of the data presented in Fig. 7 shows that the synergism obtained with the ligand-immunogen conjugate in combination with cytokines is an effect which is much greater than the sum of each of the individual effects taken separately. As discussed in Example 7 (page 22, lines 11-13 of the specification), the median survival times for the groups treated with the cytokine alone and the ligand-immunogen conjugate alone were increased over the control group by 1 and 4 days, respectively. In contrast, the median survival time for the group

treated with the ligand-immunogen conjugate and cytokines in combination was increased over the control group by 24 days (*i.e.*, a 5-fold synergism compared to the additive median survival times for the groups treated with the cytokine or the ligand-immunogen conjugate alone). Accordingly, the synergistic effect observed with Applicants' claimed methods and compositions is an effect which is much greater than the sum of each of the effects taken separately, and, under MPEP § 716.02(a), a strong synergistic effect has been obtained with Applicants' claimed invention.

The method described and claimed in the present application is now in Phase I clinical trials as a cancer therapy, and, in assays performed by the inventors and by employees of the licensee, for submission to the FDA in Investigational New Drug Study Reports, even more potent synergistic effects have been obtained, and these potent synergistic effects are consistently obtained. For example, in mice treated with the compositions and methods of the present invention, 80-100% of the mice have been completely cured. The median survival time cannot be determined when complete cures occur (*i.e.*, there is no median survival time). Thus, the synergism obtained with ligand-immunogen conjugates in combination with cytokines is infinitely large compared to the sum of the individual effects of the conjugate and the cytokine taken separately, both having minor effects. Accordingly, the synergism obtained with Applicants' claimed methods and compositions is a very potent synergism.

The Federal Circuit in *In re Dillon* concluded that a *prima facie* case of obviousness can be rebutted by "showing that the claimed compositions possess *unexpectedly improved properties or properties that the prior art does not have.*" *In re Dillon*, 919 F.2d 688, 692, 16 U.S.P.Q. 2d 1897, 1901 (Fed. Cir. 1990). (emphasis added). The prior art does not have the properties of Applicants' claimed invention because the ligand-immunogen conjugates of Cowan were never combined with the cytokines described in Smith and Insel. Furthermore, none of the cited references makes any mention that a synergistic effect, in

particular, an infinitely large synergistic effect (*i.e.*, complete cures), could be obtained with ligand-immunogen conjugates and cytokines in destroying cancer cells as is obtained with Applicants' claimed invention. Thus, the extremely potent synergism obtained with the presently claimed methods and compositions are properties that the cited prior art does not have and are unexpectedly improved properties. Clearly, complete cures resulting from the synergism obtained with Applicants' claimed invention are unexpected results, particularly when no synergistic effects were reported in the prior art. Accordingly, even if the Examiner has made a *prima facie* case of obviousness, and Applicants contend that the Examiner has not, the Applicants have rebutted the Examiner's *prima facie* case by demonstrating that Applicants' claimed methods and compositions have unexpectedly improved properties that the prior art does not have.

Moreover, at the time the invention was made it was not obvious to a person of ordinary skill in the art to practice Applicants' claimed method. For example, clinical trials had been conducted before the present invention was made to test the efficacy in cancer therapy of MOv18 and MOv19, antibodies directed against the folate receptor. Cytokines were not used in the MOv18 and MOv19 trials. More particularly, one of the references cited by the Examiner in this office action is Pouletty (reference AN). This reference was published in 1998 and describes a therapy that can be used to treat cancer that employs ligand-immunogen conjugates. There is no suggestion of using cytokines in Pouletty in combination with ligand-immunogen conjugates. If it was obvious to the skilled artisan to use ligand-immunogen conjugates in combination with cytokines, cytokines would have been used because there is unquestionably a long-felt need for improved cancer therapies. Therefore, it was not obvious at the time the invention was made to a person having ordinary skill in the art to use cytokines in folate receptor-based therapies or therapies employing ligand-immunogen conjugates.

Accordingly, it could not have been obvious at the time the invention was made that ligand-immunogen conjugates would act synergistically with cytokines in causing the extremely potent stimulation of endogenous immune responses that results from Applicants' claimed method. In particular, the strong synergism (*i.e.*, complete cures) that has been demonstrated using Applicants' claimed method was clearly an unexpected result because 1.) there was no description in the prior art at the time the invention was made of the use of any ligand-immunogen conjugate in combination with any cytokine, 2.) there was no suggestion in the prior art of any synergism between a ligand-immunogen conjugate and a cytokine, and 3.) there was no suggestion in the prior art of the extremely potent synergistic effect observed with Applicants' claimed method (*i.e.*, a synergistic effect that is so potent that 80-100% of mice are now being completely and consistently cured). Clearly, the large synergistic effect observed using Applicants' claimed method is an unexpected result when compared to the results achieved by the prior art since no results were achieved in the prior art. Withdrawal of the rejection of amended claims 43, 45, and 46 under 35 U.S.C. § 103(a) over Cowan in view of Smith and Insel is respectfully requested.

Claims 1, 8, 13, 18-26, 28-35, 38, and 43 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Pouletty in view of Smith and Insel and Mazzoni et al. The Examiner contends that Pouletty discloses the use of a composition containing a ligand-immunogen conjugate to target cancer cells, and that Smith, Insel, and Mazzoni disclose the administration of cytokines. Thus, the Examiner's arguments in support of this rejection are similar to those set forth in the rejection over Cowan in view of Smith and Insel. Applicants' arguments in response to the rejection over Cowan in view of Smith and Insel apply with equal force to the rejection over Pouletty, Smith, Insel, and Mazzoni. In particular, none of the cited references describes the use of a ligand-immunogen conjugate in combination with a cytokine, and no synergistic effects are described. An extremely potent synergism resulting in 80-100% complete cures is clearly an unexpected result compared to the cited art.

Withdrawal of the rejection of amended claims 1, 8, 13, 18-26, 28-35, 38, and 43 under 35 U.S.C. § 103(a) over Pouletty, Smith, Insel, and Mazzoni is respectfully requested.

Claims 1, 8-10, 13, 18-26, 28-35, 38, 41-43, 45, 46, 48-51, and 54 stand rejected as being unpatentable under 35 U.S.C. § 103(a) over Pouletty in view of Leamon et al. and Smith and Insel and Mazzoni et al. Claims 48 and 49 have been canceled without prejudice. The Examiner contends that Pouletty discloses the use of a composition containing a ligand-immunogen conjugate to target cancer cells, and that Smith, Insel, and Mazzoni disclose the administration of cytokines. According to the Examiner, Leamon discloses peptides linked to folic acid through either the alpha or gamma carboxyls of the glutamyl moiety of folic acid. The Examiner's arguments in support of this rejection are similar to those set forth in the rejection over Cowan in view of Smith and Insel. Applicants' arguments in response to the rejection over Cowan in view of Smith and Insel apply with equal force to the rejection over Pouletty, Smith, Insel, and Mazzoni. Withdrawal of the rejection of amended claims 1, 8-10, 13, 18-26, 28-35, 38, 41-43, 45, 46, 50-51, and 54 under 35 U.S.C. § 103(a) over Pouletty, Smith, Insel, and Mazzoni is respectfully requested.

Claims 1, 8, 13, 18-35, 38, 43, 45, 46, 48-51 and 54 stand rejected as being unpatentable under 35 U.S.C. § 103(a) over Pouletty in view of Smith and Insel and Mazzoni et al. and further in view of Cady et al. or Schroder or Modi. Claims 48 and 49 have been canceled without prejudice. The Examiner contends that Pouletty discloses the use of a composition containing a ligand-immunogen conjugate to target cancer cells, and that Smith, Insel, and Mazzoni disclose the administration of cytokines. Thus, the Examiner's arguments in support of this rejection are similar to those set forth in the rejection over Cowan in view of Smith and Insel. Applicants' arguments in response to the rejection over Cowan in view of Smith and Insel apply with equal force to the rejection over Pouletty, Smith, Insel, and Mazzoni. Cady et al. or Schroder or Modi disclose prolonged release dosage forms and do not overcome the insufficiencies of Pouletty, Smith, Insel, and Mazzoni. Withdrawal of the

rejection of amended claims 1, 8, 13, 18-35, 38, 43, 45, 46, 50-51 and 54 under 35 U.S.C. § 103(a) over Pouletty, Smith, Insel, and Mazzoni is respectfully requested.

Claims 43, 45, 46, and 50-52 stand rejected as being unpatentable under 35 U.S.C. § 103(a) over Cowan in view of Smith and Insel and further in view of Easty et al. and Walker-Daniels et al. Claim 52 has been canceled without prejudice. The Examiner contends that Cowan discloses the use of a composition containing a ligand-immunogen conjugate to target cancer cells, and that Smith and Insel disclose the administration of cytokines. Thus, the Examiner's arguments in support of this rejection are similar to those set forth above in the rejection over Cowan in view of Smith and Insel. Claim 52 has been canceled so Easty and Walker-Daniels are not applicable. Applicants' arguments in response to the rejection over Cowan in view of Smith and Insel apply with equal force to this rejection. Withdrawal of the rejection of amended claims 43, 45, 46, and 50-51 under 35 U.S.C. § 103(a) is respectfully requested.

Claims 1, 8, 13, 18-26, 28-35, 38, 43, 45, 46, 48-52 and 54 stand rejected as being unpatentable under 35 U.S.C. § 103(a) over Pouletty in view of Smith and Insel and Mazzoni et al. and further in view of Easty et al. and Walker-Daniels et al. Claims 48, 49, and 52 have been canceled without prejudice. The Examiner contends that Pouletty discloses the use of a composition containing a ligand-immunogen conjugate to target cancer cells, and that Smith, Insel, and Mazzoni disclose the administration of cytokines. Thus, the Examiner's arguments in support of this rejection are similar to those set forth in the rejection over Cowan in view of Smith and Insel. Applicants' arguments in response to the rejection over Cowan in view of Smith and Insel apply with equal force to the rejection over Pouletty, Smith, Insel, and Mazzoni. Easty et al. and Walker-Daniels et al. are directed to claim 52 so these references are not applicable. Withdrawal of the rejection of amended claims 1, 8, 13, 18-26, 28-35, 38, 43, 45, 46, 50-51, and 54 under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

The foregoing amendments and remarks are believed to fully respond to the Examiner's rejection. The amended claims are in condition for allowance. Applicants respectfully request allowance of the claims, and passage of the application to issuance.

Respectfully submitted,

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